BILLING CODE: 4140-01-P

DEPARTMENT: DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health

ACTION: Notice

SUMMARY: The invention listed below is owned by an agency of the U.S. Government and is available for licensing and/or co-development in the U.S. in accordance with 35 U.S.C. 209 and 37 CFR part 404 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing and/or co-development.

ADDRESSES: Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702.

FOR FURTHER INFORMATION CONTACT: Information on licensing and co-development research collaborations, and copies of the U.S. patent applications listed below may be obtained by contacting: Attn. Invention Development and Marketing Unit, Technology Transfer Center, National Cancer Institute, 9609 Medical Center Drive, Mail Stop 9702, Rockville, MD, 20850-9702, Tel. 240-276-5515 or email ncitechtransfer@mail.nih.gov. A signed Confidential Disclosure Agreement may be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: Technology description follows.

Title of invention:

Analogues of Withanolide E Sensitize Cancer Cells to Apoptosis

Keywords: TRAIL, TLR3, apoptosis, immunotherapy, tumor necrosis factor, TNF

Description of Technology:

The tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) protein has been a target of interest in cancer therapy because it plays a large role in inducing cell apoptosis in cancer cells but not in normal cells. Although TRAIL has been reported to successfully target certain tumor cells which are resistant to traditional chemotherapy or radiation, TRAIL resistance has also been widely observed. Similarly, Toll-like receptor (TLR) 3 ligands such as poly I:C have also been reported to promote apoptosis in certain cancer cells, though the apoptotic signaling in most cancer cells was weak and was only significant following longer term incubations. Thus, there is a need to develop compounds that can sensitize cancer cells to apoptosis inducing ligands, such as poly I:C and TRAIL.

In collaboration with the University of Arizona, NCI investigators have discovered a series of compounds in the withanolide family that synergistically enhance the response of cancer cells to treatment with an apoptosis-inducing ligand. The compounds each show a 4- to 10-fold increase in potency compared to withanolide E alone in promoting death ligand-mediated cancer cell death. One biotinylated analogue in particular is at

least 15-fold more potent than withanolide E in promoting apoptosis in human melanoma cells when used in combination with either poly I:C or TRAIL. A selection of active compounds were tested in murine xenograft models of human melanoma and showed decreased tumor growth and tumor regression.

Potential Commercial Applications:

- Potential therapeutic for the treatment of cancer either alone or in combination with an apoptosis inducing agent such as TRAIL receptor or TLR 3 agonists by directly promoting tumor cell apoptosis.
- Possible indirect enhancement of cancer immunotherapy due to release of cancer cell antigens in the presence of the powerful immune-adjuvant effects of TLR3 agonists.

Value Proposition:

- Withanolide E derivatives enhance the anti-cancer activity of known apoptosis inducing ligands such as TRAIL or poly I:C and may be used to enhance efficacy of TRAIL receptor or poly I:C agonists that are currently under development.

Development Stage:

Pre-clinical (in vivo validation)

Inventor(s):

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(NCI), James McMahon (NCI), Leslie Gunatilaka (University of Arizona), Ya-ming Xu (University of Arizona), and E.M. Kithsiri Wijeratne (University of Arizona)

Intellectual Property:

US Provisional Application No. 62/292,974, entitled "Method of Sensitizing Cancer Cells to The Cytotoxic Effects of Apoptosis Inducing Ligands in Cancer Treatment," filed February 9, 2016

Publications:

1. Tewary P., Gunatilaka A.A. and Sayers T.J. (2016) Using natural products to promote caspase-8-dependent cancer cell death. Cancer Immunol Immunother. doi:10.1007/s00262-016-1855-0

Related Technologies: US Patent 9,238,069 (HHS Ref. No. E-050-2010) entitled "Use of withanolides to sensitize cancer cells to the cytotoxic effects of Apo2L/TRAIL" issued January 19, 2016.

Collaboration Opportunity: Researchers at the NCI seek licensing and/or co-development research collaborations for development of withanolide E analogues for the treatment of cancer.

Contact Information:

Requests for copies of the patent application or inquiries about licensing, research collaborations, and co-development opportunities should be sent to John D. Hewes, Ph.D., email: john.hewes@nih.gov.

Dated: September 6, 2016

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